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National Cancer Institute

Cancer of the Uterus

Research Report

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Introduction

This *Research Report* describes current research on the causes and prevention, symptoms, diagnosis, and treatment of cancers of the *uterine cervix* and the *uterine corpus,* or endometrium. The information presented here was obtained from recent articles in the scientific literature, discussions with National Cancer Institute (NCI) scientists and other researchers, and various scientific meetings.

This *Report* provides more detailed information than is contained in the patient-oriented pamphlets, *What You Need to Know About Cancer of the Uterus* and *What You Need to Know About Dysplasia, Very Early Cancer and Invasive Cancer of the Cervix.*

Description and Function of the Uterus

The uterus, or womb, is located in the female pelvis. Under normal circumstances, the uterus is hollow and about the size and shape of an inverted pear. The broad upper part is called the corpus; the lower, narrow end is the cervix. During pregnancy, the uterus expands as the fetus grows within it.

The walls of the uterus are composed of muscular tissue called the myometrium, which is lined with a membrane called the endometrium. Cancer of the uterus most often develops in the cervix or in the endometrium of the corpus.

Endometrial and cervical cells normally grow and are replaced in an orderly, controlled pattern. When cell division is disordered, masses of tissue, called tumors, begin to grow. Such tumors may be benign or cancerous.

Benign uterine tumors, or fibroids, do not spread to nearby tissues or organs. They often cause no symptoms and require no treatment. If fibroids cause pain or bleeding, they may be removed completely by surgery.

In contrast, endometrial and cervical cancers invade and destroy nearby tissues and organs and can spread, or metastasize, to other parts of the body. When they begin to spread outside of the uterus, these cancer cells usually travel through the lymphatic system rather than the bloodstream. Lymph nodes scattered along the vessels of the lymphatic system collect and filter lymph fluid. The nodes filter out abnormal substances, including cancer cells. For this reason, lymph nodes near the tumor site are often removed during surgery so that a pathologist can examine them for evidence of cancer cells.

Cancer of the Cervix

Incidence

Cancer of the cervix accounts for 6 percent of all cancers in women and occurs most often in women between the ages of 40 and 60. In 1986, about 14,000 cases of cervical cancer will be diagnosed in the United States, and the disease will cause approximately 6,800 deaths. From 1950 to 1970, the incidence and mortality rates of invasive cervical cancer fell by more than 50 percent. Both rates have continued to drop since 1970, due mainly to the success of screening programs in bringing about earlier detection and treatment.

Cause and Prevention

Some women are more likely than others to develop abnormal cervical cells. Such women are considered to be "at risk," which means that their chances of developing cervical cancer are higher than average. The incidence of cervical cancer is higher than average among women of low income, women who began having sexual intercourse before age 18, and women who have had many sex partners. The daughters of women who took the drug diethylstilbestrol (DES) during pregnancy are also at risk. In a small number of such daughters, DES and some similar drugs have been linked to abnormal tissue formations in the vagina and cervix, including a rare type of vaginal and cervical cancer. Women on menopausal estrogen therapy and women who have had no children have a lower-than-average risk of developing cervical cancer.

There is also some suspicion that cervical cancer may be associated with venereal disease. This suspicion has been strengthened by the finding that increased levels of antibodies to genital herpes virus have been found in some women with cervical cancer, indicating that they were exposed to the virus.

Recent research indicates that another type of virus, a papillomavirus, may play a role both in the development of cervical dysplasia (abnormal cells) and the transformation of dysplasia into cancer. Papillomavirus infection is associated with flat genital warts, or condylomas, which may be precursors of dysplasia. In addition, papillomavirus proteins have been found in a large percentage of dysplastic tissue samples. Most scientists believe that several agents are necessary to cause dysplasias to progress into cancers, but some now believe that the initiating factor may be the human papillomavirus.

Type of contraception is related to cervical cancer incidence: more cervical cancer is seen among women who use oral contraceptives, less among those who use barrier methods, like the diaphragm. This may be because barrier methods protect against venereal infection, or because women who use oral contraceptives may be more sexually active.

The circumcision status of a sexual partner has not been found to increase cervical cancer risk.

Smoking does increase risk, although scientists are unable to explain how this occurs biologically.

In studies with laboratory animals, scientists have discovered that vitamin A plays a role in arresting or preventing cancerous changes in epithelial cells, the cells that line the interior and exterior surfaces of the body. Synthetic forms of vitamin A (retinoids), which produce fewer side effects than vitamin A when given in large doses, are currently being tested in populations at high risk of developing cancer. In one such study, women with cervical dysplasia, who are at high risk of developing invasive cervical cancer, are receiving a retinoid-containing vaginal salve. Although studies like these may lead to new methods of preventing cervical cancer, presently the most effective means of prevention is the surgical removal of precancerous tissue.

Detection of Cervical Cancer

Often, cervical cancer does not have any symptoms. The most common symptom is abnormal vaginal bleeding (bleeding that starts and stops between regular menstrual periods or bleeding that occurs after intercourse or after a gynecological examination). An increased vaginal discharge is another common symptom. These are not sure signs of cancer, but they do indicate the need for further tests, including a complete pelvic examination and Pap smear.

Regular, complete pelvic examinations and Pap smears are the best way to detect cervical cancer and precancerous conditions early. A pelvic exam involves physical examination of the organs in the pelvic area, including the uterus, vagina,

ovaries, fallopian tubes, bladder, and rectum. A speculum is used to hold the vagina open so that the physician can view the upper portion of the vagina and the opening of the cervix. A Pap test consists of the collection of a sample of cells (a smear) from the cervix and examination of these cells under a microscope. The presence of abnormal cells is not proof of cervical cancer or even of a precancerous condition, but it does indicate the need for further tests.

A National Institutes of Health Consensus Development Conference recommended that all women who have had sexual intercourse should begin a regular screening program for cervical cancer. If the first Pap smear does not show any abnormal cells, it should be repeated in 1 year. If the second smear also is negative, the test should be repeated at regular intervals of 1 to 3 years. The decision on how often to retest should be made jointly by a woman and her physician. With the exception of DES daughters, who should be examined at least once a year after the onset of menstruation, virgins need not be screened for cervical cancer.

The Pap test sometimes fails to pick up cancer cells. The possibility of such "false negative" results is one reason why women should have Pap tests and pelvic exams regularly. The Pap test can detect dysplasia and carcinoma *in situ,* two symptom-free conditions that sometimes develop into invasive cervical cancer. Both conditions are almost 100 percent curable if treated promptly. Dysplasia and carcinoma *in situ* are types of cervical intraepithelial neoplasia (CIN). Mild dysplasia is classified as CIN I, moderate dysplasia as CIN II, and severe dysplasia and carcinoma *in situ* as CIN III. A pathologist classifies dysplastic cells on the basis of microscopic cellular characteristics.

Dysplasia, the development of abnormal cells, is not a cancerous condition. Although dysplastic cells have the same general microscopic appearance as cancerous cells, dysplastic cells do not invade underlying tissue. The term "atypical hyperplasia" is sometimes used to indicate the proliferation of dysplastic cells. Dysplasia occurs most often in women between the ages of 25 and 35, but it can appear in younger women.

Mild dysplasia may not require treatment, but it should be checked regularly for an increase in severity. Moderate dysplasia is usually treated by cryotherapy or cauterization. Cryotherapy destroys abnormal tissue by freezing it; cauterization involves the use of heat. Severe dysplasia may require the surgical removal of abnormal tissue in a procedure called conization, the excision of a small cone-shaped piece of tissue from the cervix. These procedures are frequently done in the doctor's office and do not require a hospital visit.

Carcinoma in situ, also called very early cancer, is cancer that has not spread below the lining of the first layer of cervical tissue. Carcinoma *in situ* is the earliest form of cervical cancer that can be detected. It is most common in women between the ages of 30 and 40, although it can develop in women of other ages.

Cryosurgery, cauterization, or surgical conization may be used to treat carcinoma *in situ.* Conization is the usual treatment for young women who wish to have children. In women who no longer wish to bear children, a hysterectomy, the surgical removal of the uterus, may be performed. This surgery eliminates the possibility that uterine cancer will develop later in life.

Recently, lasers have been used to destroy abnormal cervical tissue. (The word "laser" stands for "light amplification by stimulated emission of radiation.") The laser is a device that transforms light waves into a powerful beam that can be used in some surgical procedures instead of a scalpel. Although preliminary results have been very good, the evidence is not yet conclusive that laser surgery is better than current methods of treatment for early cervical cancer.

Diagnosis of Cervical Cancer

If the doctor's inspection or the Pap smear shows any abnormality, a biopsy—the removal of a tiny amount of suspicious tissue—is usually done. Doctors use several methods to identify areas of suspicious tissue for biopsy. With the Schiller's test, iodine is applied to the surface of the cervix. Normal cells are stained by the iodine; areas not stained are then biopsied. Doctors may also use a colposcope, which magnifies the view of the cervix and vagina, to inspect suspicious areas more closely. If a vaginal infection is suspected as the cause of the abnormal smear, the smear may simply be repeated after treatment of the infection.

If the biopsy and Pap smear results are abnormal, or if the

two tests give conflicting results, larger tissue samples may be required for an accurate diagnosis. These are obtained most often by conization or dilatation and curettage (D and C). In a D and C, the cervix is dilated to permit insertion of a curette, a small instrument that gently scrapes material from the uterine lining.

Examination of tissue samples from biopsy, conization, or D and C may reveal dysplasia, carcinoma *in situ,* cervical cancer, or other diseases. If evidence of cancer is found, further tests are done to determine its extent. The most important of these tests is a more thorough pelvic examination, including inspection of the abdomen, vagina, and rectum. A doctor can often feel a tumor or detect tenderness caused by a tumor in these areas. Cancer spreads to distant parts of the body, most often to the lung, in only about 15 percent of cervical cancer patients. Staging is a system used to describe the degree to which the cancer has spread:

Stage 0: Carcinoma *in situ*

Stage I: Carcinoma confined to the cervix

Stage II: Carcinoma extends beyond the cervix but not to the pelvic wall

Stage III: Carcinoma extends to the pelvic wall

Stage IV: Carcinoma extends beyond the pelvis or invades the bladder or rectum

Almost all cervical cancers are squamous cell carcinomas. Squamous cells are a type of epithelial cell; any cancer that originates in epithelial cells is called a carcinoma.

Treatment of Cervical Cancer

The choice of treatment for cervical cancer depends on the patient's general condition and on the stage of the disease. In its early stages, cervical cancer is usually treated with surgery or radiation or a combination of the two. Chemotherapy (treatment with anticancer drugs) is often recommended for later stages of the disease.

Stage I cervical cancer can be effectively treated with either surgery or radiation therapy. Surgery is often selected in younger women because it preserves the hormone-producing function of the ovaries. Surgical treatment consists of a hysterectomy, the removal of the entire uterus, including the cervix. The two types of treatment are equally effective, with cure rates of 85 to 90 percent.

In older women, radiation may be selected because it is more easily tolerated than surgery, particularly if other medical problems are present. Surgery may also be used in combination with radiotherapy if the shape of the tumor in the cervix makes insertion of radioactive implants (described below) difficult.

Most patients in whom the disease has progressed beyond stage I are treated with radiotherapy alone. However, if the cancer has spread minimally to the vagina (early Stage II), surgery may be selected for patients who are young and in good general health. The surgical procedure most often used is the radical hysterectomy, involving removal of the upper part of the vagina and nearby tissues and lymph nodes as well as the uterus.

Radiation treatment usually consists of a combination of external and internal radiation. X-rays from a linear accelerator or gamma rays from a cobalt source may be beamed through the body to the tumor site. Treatments of this kind are usually given (on an outpatient basis) over a period of several weeks.

Radiation may also be applied directly to the cervix by inserting, through the vagina, tiny metal cylinders containing a radioactive element, such as radium or cesium. The cylinders are usually left in place for 2 or 3 days. Patients receiving internal irradiation are hospitalized for several days.

If the cancer has spread extensively or has reappeared after initial treatment with surgery or radiation therapy, chemotherapy may be prescribed. In such cases, anticancer drugs frequently are injected into the bloodstream, often in an outpatient setting. There is currently no standard treatment for stage IV cervical cancer, but many new regimens are being evaluated in clinical trials.

Several current studies are evaluating the effectiveness of various anticancer drugs, alone and in combination with other drugs and/or radiation. Drugs used in combination chemotherapy protocols, or research programs, include cisplatin (Platinol), bleomycin, mitomycin (Mitomycin-C), vincristine, methotrexate, and doxorubicin (Adriamycin), usually in combinations of two or three.

Other investigational treatments of cervical cancer include immunotherapy and the use of

radiation sensitizers. Immunotherapy is the use of drugs that stimulate the body's immune system to fight off disease. In treating cervical cancer, the immunotherapeutic agent most often used is the bacterium *C. parvum*. Immunotherapy is usually given in combination with radiation or chemotherapy. Radiation sensitizers are drugs such as misonidazole and hydroxyurea which, when given before the administration of radiation, are believed to make cancerous cells more sensitive to the radiation.

Endometrial Cancer

Incidence

Endometrial cancer occurs most often in women between the ages of 55 and 70 and accounts for 13 percent of all cancers in women. In the United States, an estimated 36,000 new cases of endometrial cancer will be diagnosed in 1986, and the disease will cause around 2,900 deaths. From 1950 to 1970, the death rate from endometrial cancer fell more than 50 percent; since then, it has continued to decline. The incidence, which increased fairly rapidly from 1969 to 1976, has since been falling. This observation has been explained by a similar rise and fall in the use of menopausal estrogen therapy, which has since been shown to increase the risk of endometrial cancer.

Cause and Prevention

Although no direct cause of endometrial cancer has yet been found, a variety of factors appear to increase a woman's chances of developing endometrial cancer. Among these so-called risk factors are obesity, diabetes, infertility, and late menopause. As mentioned above, there is also a small but significant increase in risk associated with the use of estrogen replacement therapy to relieve the symptoms of menopause.

The use of certain oral contraceptives actually appears to lower the risk of endometrial cancer. The rate of endometrial cancer among women who have used oral contraceptives containing both estrogen and progesterone, two female hormones, is only about half the rate of women who have never used these drugs. The risk appears to decline with increasing duration of contraceptive use, and the reduced risk seems to persist for several years after use. The reduction in overall incidence is small, however, because endometrial cancer is uncommon in women of childbearing age.

As with cervical cancer, the most promising method of preventing invasive endometrial cancer is early detection and treatment of precancerous conditions. The most common precursor of invasive endometrial cancer is endometrial hyperplasia.

Detection of Endometrial Cancer

Abnormal vaginal bleeding after menopause is the most common symptom of endometrial cancer. The bleeding may start as a watery, blood-streaked discharge, but it eventually contains more blood. A bloody discharge does not always mean that cancer is present, but it does indicate the need for further tests to rule out the possibility of cancer.

Endometrial hyperplasia, the proliferation of endometrial tissue, is generally considered a precancerous condition similar to cervical dysplasia. The usual symptom of hyperplasia is irregular and occasionally profuse uterine bleeding. Like dysplasia, hyperplasia may be mild, moderate, or severe. Severe hyperplasia is often called carcinoma *in situ* of the endometrium. Unlike cervical dysplasia, however, there is no reliable method of screening symptom-free women for endometrial hyperplasia, so this condition is usually not detected until symptoms are present. The Pap smear is not an accurate test for hyperplasia or endometrial cancer, because abnormal endometrial cells often lose their characteristic features before they reach the vagina, where cells for the Pap smear are collected. The American Cancer Society recommends that women at high risk of endometrial cancer have an endometrial biopsy at menopause.

Treatment of endometrial hyperplasia depends largely on the stage of the disease and the age of the patient. In young women, endometrial hyperplasia often is associated with irregular menstrual cycles. These patients are usually given female hormones to induce regular cycles, and the endometrial tissue is sampled frequently to monitor the success of the treatment.

Endometrial hyperplasia in women near menopause is treated with progesterone if the condition is not severe. Hysterectomy, surgical removal of the uterus, is the usual treatment for severe cases, and is also recom-

mended for postmenopausal women with hyperplasia. If other medical problems make the patient a poor candidate for surgery, progesterone therapy usually is prescribed.

Diagnosis of Endometrial Cancer

When symptoms suggest endometrial cancer, a biopsy or D and C usually is performed. A biopsy entails the removal of a small amount of suspicious tissue, while dilatation and curettage (D and C) is used to obtain a larger tissue sample. The D and C entails dilating the cervix and removing a small sample of tissue from the lining of the uterus. Examination of tissue samples from a biopsy or D and C may reveal hyperplasia, endometrial cancer, or other diseases. If there is evidence of cancer, other tests are performed to determine the extent of the disease.

Results of a D and C may indicate that the cancer has spread to the cervix; this occurs in 10 to 15 percent of women with endometrial cancer. If the cancer has spread further, the extent of metastasis is determined by a thorough pelvic exam and the use of endoscopic techniques, which allow a doctor to look directly at tissues within the body, and radiographic techniques, such as X-rays. Metastases to distant parts of the body are uncommon in endometrial cancer. Tumors in the lung, the most common site of distant metastasis, appear in only 2 to 3 percent of patients. The following staging system is used to describe the degree to which the cancer has spread:

Stage 0: Carcinoma *in situ*

Stage I: Carcinoma is confined to uterine corpus

Stage II: Carcinoma involves corpus and cervix but has not extended outside the uterus

Stage III: Carcinoma extends beyond the uterus but not outside the pelvis

Stage IV: Carcinoma extends beyond the pelvis or involves the bladder or rectum

Five cell types of endometrial carcinoma have been reported, but one type, adenocarcinoma, accounts for more than 90 percent of all cases.

Treatment of Endometrial Cancer

The choice of treatment for endometrial cancer depends on the patient's general condition and on the stage of the disease. In its early stages, endometrial cancer is usually treated with surgery or radiation or a combination of the two. Hormone therapy is often recommended for later stages of the disease.

Surgery for endometrial cancer entails not only the removal of the uterus (hysterectomy), but often the removal of the ovaries and fallopian tubes as well, a procedure called bilateral salpingo-oophorectomy. Surgery is the usual treatment for stage I endometrial cancer, with radiation therapy given in addition if the tumor is growing rapidly.

If the cancer has spread to the cervix (stage II), some physicians recommend radiation therapy to the entire pelvis followed by a hysterectomy. Others prefer to evaluate the surgical specimen and recommend postoperative irradiation for patients whose tumors appear likely to recur.

As with cervical cancer, radiation for endometrial cancer may be administered either externally or internally. External irradiation usually consists of X-rays or gamma rays, which may be beamed through the body to the tumor site. These treatments are most often given on an outpatient basis over a period of several weeks.

Patients receiving internal irradiation are usually hospitalized during treatment. This form of radiotherapy is delivered by inserting, through the vagina, tiny metal cylinders containing a radioactive element such as radium or cesium. The cylinders are usually left in place for 2 or 3 days.

In stage III, when the tumor extends outside the uterus but is still confined to the pelvis, standard treatment involves radiation. Patients who are not candidates for surgery or radiotherapy often benefit from progesterone.

Administration of progesterone is the traditional treatment for metastatic endometrial cancer; approximately 30 to 40 percent of patients respond, with responses sometimes lasting years. Synthetic forms of progesterone include hydroxyprogesterone (Delalutin), medroxyprogesterone (Provera), and megestrol (Megace).

Treatment with anticancer drugs (chemotherapy) for patients with advanced disease currently is being tested. Doxorubicin (Adriamycin) appears to be the single most effective

drug. Studies of several combinations of commonly used drugs, including doxorubicin and cyclophosphamide (Cytoxan), have also produced encouraging results.

PDQ

The National Cancer Institute has developed PDQ (Physician Data Query), a computerized database designed to give doctors quick and easy access to:

- the latest treatment information for most types of cancer;
- descriptions of clinical trials that are open for patient entry; and
- names of organizations and physicians involved in cancer care.

To get access to PDQ, a doctor may use an office computer with a telephone hookup and a PDQ access code, or the services of a medical library with on-line searching capability. Most Cancer Information Service offices (1-800-4-CANCER) provide a physician with one free PDQ search, and can tell doctors how to get regular access to the database. Patients may ask their doctor to use PDQ or may call 1-800-4-CANCER themselves. Information specialists at this toll-free number use a variety of sources, including PDQ, to answer questions about cancer prevention, diagnosis, and treatment.

Suggestions for Additional Reading

Except as noted, the following materials are not available from the National Cancer Institute. They can be found in medical libraries, many college and university libraries, and some public libraries. Information about ordering NCI materials is provided at the end of this publication.

Chemotherapy and You: A Guide to Self-Help During Treatment, prepared by the Office of Cancer Communications, National Cancer Institute. NIH Publication No. 85-1136.

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Nelson, J.H., Jr. et al. "Detection, Diagnostic Evaluation and Treatment of Dysplasia, Carcinoma in situ and Early Invasive Cervical Carcinoma," *Ca—A Cancer Journal for Clinicians,* 29(3), 1979, pp. 174-192.

Oral Contraceptives and Cancer Risk, a Fact Sheet prepared by the Office of Cancer Communications, National Cancer Institute, 1985.

Radiation Therapy and You: A Guide to Self-Help During Treatment, prepared by the Office of Cancer Communications, National Cancer Institute. NIH Publication No. 85-2227.

Tsukamoto, N. "Treatment of Intraepithelial Neoplasia with the Carbon Dioxide Laser," *Gynecologic Oncology,* 21(3), 1985, pp. 331-336.

What Are Clinical Trials All About?, prepared by the Office of Cancer Communications, National Cancer Institute. NIH Publication No. 85-2706.

Additional Information

For additional information on this subject and for other NCI publications, write to the Office of Cancer Communications, National Cancer Institute, Bethesda, MD 20892, or call the Cancer Information Service toll-free at

1-800-4-CANCER*

*In Alaska call 1-800-638-6070; in Hawaii, on Oahu call 524-1234 (call collect from neighbor islands).

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